Guidance for Industry

Microbiological Data for Systemic Antibacterial Drug Products — Development, Analysis, and Presentation

DRAFT GUIDANCE

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For questions regarding this draft document contact Fred Marsik at 301-796-0756.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

September 2009
Clinical Antimicrobial

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Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, rm. 2201
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Tel: 301-796-3400; Fax: 301-847-8714; E-mail: druginfo@fda.hhs.gov
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Guidance for Industry[1]
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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

The purpose of this guidance is to inform industry of the Food and Drug Administration's (FDA's) current thinking regarding the types of microbiological studies, assessments, and clinical trials needed to support an investigational new drug application (IND) and a new drug application (NDA) for a systemic antibacterial drug product.[2] This guidance is intended to serve as a focus for continued discussions among the Office of Antimicrobial Products, pharmaceutical sponsors and applicants, the academic community, and the public.[3] Recommendations in this guidance cover three major areas: (1) conducting general nonclinical studies; (2) conducting animal and human studies and clinical trials; and (3) establishing and updating in vitro susceptibility test methods, quality control parameters, and interpretive criteria. This guidance also recommends the content and format for presentation of microbiological data for antibacterial drug products in the Microbiology subsection of labeling (see Appendix A).

This guidance does not address the development of antiviral, antifungal, antiparasitic, or antimycobacterial agents or antibacterials administered by nonsystemic routes (e.g., topical). This guidance is not meant to provide details on clinical trial design.

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[1] This guidance has been prepared by the Office of Antimicrobial Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* and *drug products* include both human drugs and therapeutic biological products unless otherwise specified.

[3] In addition to consulting guidances, sponsors and applicants are encouraged to contact the division to discuss specific issues that arise during the development of antimicrobial drug products.

As the science of clinical microbiology and the development of antibacterial drug products evolve, this guidance will be revised.[4] We recognize that the results of in vitro susceptibility testing are not absolute for a variety of clinical and technical reasons and are meant only to guide treatment. The accuracy and clinical relevance of such tests depend on adherence to standardized methods and appropriate consideration of the test results.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

In vitro microbiological data and in vivo animal studies (e.g., spectrum of activity in vitro and appropriate animal models of human disease) support the justification of testing in humans. Generally, sponsors submit data from nonclinical investigations to provide proof of concept of clinical activity before commencing human phase 2 clinical trials and to aid in the development of provisional interpretive criteria for use in phase 3 clinical trials. Microbiological data submitted to an NDA will be used to substantiate the microbiological information contained in the labeling for human prescription drugs and biological products (labeling).[5]

This guidance discusses the following specific microbiological issues that should be addressed in the NDA:

- Spectrum of antimicrobial activity

- Other anti-infective properties (e.g., mechanism of action, mechanism of resistance, activity in the presence of body fluids, development of hetero-resistance)

- Methods for in vitro susceptibility testing

- Proposed quality control (QC) for susceptibility testing

- Proposed interpretive criteria for susceptibility test results

- Information from appropriate animal models of infection that support proof of concept

- Pharmacokinetics

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[4] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[5] See 21 CFR 201.56(d) and 201.57.

- Pharmacodynamics

- In vivo and in vitro correlations relevant to the organisms and disease indications sought

- Information from clinical trials evaluating clinical outcome by baseline pathogen minimum inhibitory concentration (MIC) data

- Proposed wording in the format provided in the final rule Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products for sections of the labeling that describe microbiology[6]

III. GENERAL NONCLINICAL IN VITRO AND IN VIVO INFORMATION

This section describes the nonclinical studies that sponsors should conduct to help characterize antibacterial drug products during phase 1 and phase 2 of drug development. This section also describes the nonclinical information that applicants should submit in an NDA to support statements made in the Microbiology subsection and other sections of the labeling (see Appendix A). The goal should be to learn about a drug product's antibacterial activity in vitro and in animal models of infection (see section IV). Most studies should be done at a minimum in duplicate, with triplicate testing preferred. Some studies, such as the establishment of QC parameters for in vitro susceptibility tests and in vitro susceptibility testing, should be done with antimicrobials of certified potency in accordance with standardized procedures, such as those recommended by the Clinical and Laboratory Standards Institute (CLSI), in a number of laboratories to determine the intra- and interlaboratory reproducibility of the results.

Sponsors should design and conduct studies to achieve the following objectives:

- Specify the method by which in vitro activity of the antibacterial drug product can best be determined (e.g., microbroth dilution, disk diffusion)

- Evaluate culture and environmental conditions that may affect the assessment of in vitro antibacterial activity

- Establish QC parameters for in vitro susceptibility testing of the antibacterial drug product before determining its activity against bacterial isolates

- Demonstrate in vitro activity against target bacteria

- Determine equivalence between broth dilution and agar dilution susceptibility test results

[6] See Appendix A and 21 CFR 201.56(d) and 201.57

- Determine the in vitro activity of the antibacterial drug product in the presence of human body fluids and secretions (e.g., plasma protein, lung surfactant)

- Demonstrate the activity of the antibacterial drug product in an appropriate animal model, when available, as proof of concept that the antimicrobial drug product has in vivo activity; we suggest that sponsors conduct studies of animal models of infection with organisms similar in character (e.g., antimicrobial resistance, virulence factors) to organisms that will be targeted in humans

- Determine if interactions with other antimicrobial agents (e.g., antagonism, synergy, additive) and nonantimicrobial drugs (e.g., interference) might occur

- Provide information on mechanisms of action and on the potential for the development of resistance and cross-resistance to other antimicrobials

We recommend that sponsors provide the results of the nonclinical studies before initiation of phase 2 clinical trials in support of the establishment of provisional interpretive criteria for the pathogens under investigation. Sponsors also should consider the information from in vitro studies, animal models of infection, and pharmacokinetic/pharmacodynamic (PK/PD) information derived from animal and human studies and clinical trials in deciding the types of clinical infections for which the antibacterial drug product should be further developed.

A. Antibacterial Spectrum of Activity

Sponsors should evaluate the activity of an antibacterial drug product, including its active components and metabolites, against a test panel of microorganisms that are potential pathogens in the intended indication. The number of isolates tested and their diversity are important (e.g., geographic distribution, relevant clinical genera and species, relevant resistant mechanisms). The number of organisms, irrespective of the species, to be tested for determining the spectrum of activity of the antibacterial drug product under development as well as comparator antimicrobials should be at least 500 for both dilution and disk diffusion tests. Sponsors should provide testing data on a sufficient range of clinically relevant bacteria to allow conclusions to be made regarding the potential clinical efficacy of the antibacterial for the intended indication. We recommend that sponsors identify the prominent genotypes, serotypes, biotypes, and isolates with known mechanisms of resistance and include these in the test panel. When appropriate, the spectrum of activity against hetero-resistant bacteria should be determined (e.g., vancomycin hetero-resistant *Staphylococcus aureus*). The organisms tested should be fresh clinical isolates with susceptibility profiles that are representative of antibacterial drug products used to treat infections caused by the target pathogens for the indication being sought.

When conducting studies of the antibacterial spectrum of activity, sponsors should include FDA-approved antibacterial drug products, especially those with the same mechanism of action as the new drug product that is tested in parallel. In the case of a drug product that acts by a new mechanism of action, we recommend that sponsors include FDA-approved antibacterial drug products with the same spectrum of activity. In the event there is no FDA-approved antibacterial drug product with a similar spectrum of activity, we recommend that sponsors discuss with the FDA which approved drugs to include in studies evaluating antibacterial spectrum of activity.

Sponsors who want to include isolates of organisms from outside the United States in the overall spectrum of activity of the antibacterial drug product should show that the isolates have similar characteristics as the same organisms found in the United States, such as phenotype, genotype, serotype, susceptibility profile, and virulence factors.

We recommend that study reports of antibacterial spectrum of activity submitted to an IND or NDA include the following elements, where applicable:

- The name and location of each investigator conducting or contributing to the study; the data provided by each investigator should be identified

- The standardized and validated susceptibility testing method used to determine the activity of the antibacterial drug product; if an experimental method is used then the details of the method and the performance characteristics of the assay in the actual laboratory where such testing is done should be included

- A description of all susceptibility testing QC measures; all susceptibility test results should be accompanied by QC data

- The number of isolates tested in each laboratory and the geographical region from which the isolates were obtained

- A description of the spectrum of activity by individual geographic regions and all regions combined

- The phenotypic and/or genotypic characterization of isolates relative to their resistance to other antibacterial drug products; the methodology and the criteria used to characterize isolates as resistant should be described

- The phenotypic and/or genotypic characterization of isolates relative to virulence characteristics (e.g., *S. aureus* — Panton-Valentine Leukocidin (PVL))

- The susceptibility testing results for each organism presented in tabular form in terms of MIC; minimum bactericidal concentration (MBC) should be submitted when appropriate (e.g., treatment of meningitis)

We recommend that sponsors supplement the reports with summary data to include:

- The MIC range and the number of isolates tested
- MIC_{50}
- MIC_{90}
- MIC:MBC ratio for members of clinically relevant genera

Summary data by subset of organisms demonstrating resistance should be provided (e.g., methicillin-resistant *S. aureus*, extended spectrum β-lactamases (ESBLs)). Sponsors should present a summary of susceptibility testing results as MIC frequency distributions (e.g., histograms) displaying any proposed breakpoints.

Sponsors should provide in annual reports information that becomes available after approval relative to changes in the spectrum of activity of an antibacterial drug product. When such information warrants a change to the labeling for an antibacterial drug product, a labeling supplement should be submitted.[7]

B. Mechanism of Action

Sponsors should report what information is known about the mechanism of action of a new drug product. The report should include the drug product's chemical structure and a description of any structural or biological similarities to known antibacterial drug products. In particular, sponsors should report study results that demonstrate the mechanism of action (e.g., inhibition of cell wall synthesis, lysis of cell membrane, protein synthesis, and inhibition of DNA or RNA replication). These reports should provide data to substantiate both physiological and morphological effects on the microbial cells. Such information also can provide a basis for understanding the development of resistance through alterations in the drug product's target sites. Reports of studies evaluating microbial killing (e.g., microbial kill curves) also can be included along with reports of studies on mechanism of action.

C. Intracellular Antimicrobial Concentration Assessment

The ability of an antibacterial drug product to achieve significant intracellular concentrations may have clinical importance when the target organism can reside within the cell (e.g., *Listeria*, C*hlamydophila*, *Legionella*). In situations where the antimicrobial drug product is intended to treat infections caused by microorganisms that reside within the cell, sponsors should provide data on the drug product's ability to penetrate into host cells and demonstrate the drug product's activity inside the cell against target microorganisms.

D. Mechanism of Resistance Studies

Resistance mechanisms may limit the effectiveness of an antibacterial drug product in clinical settings. Therefore, characterization of the mechanisms mediating resistance and their distribution within the proposed target pathogens may delineate the potential clinical usefulness of the drug product. Mechanisms include alterations of the drug product by production of enzymes (e.g., β-lactamases, ESBLs), inability to reach the target, and changes in the affinity of the antibacterial for the target site. In addition, acquisition of drug resistance mechanisms might

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[7] For more information on procedures for updating susceptibility test information for antibacterial drug product labeling, see the guidance for industry *Updating Labeling for Susceptibility Test Information in Systemic Antibacterial Drug Products and Antimicrobial Susceptibility Testing Devices* on the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

affect the growth or metabolism of the cell in such a way as to change resistance to or decrease drug efficacy. To determine if there may be a proportion of bacteria in the overall population that are resistant to the antibacterial drug product (i.e., hetero-resistance), testing should be done to evaluate for the presence of such bacteria. When possible, we recommend that sponsors provide the genotypic characteristic of resistance mechanisms.

Sponsors should compare the activity of a new antibacterial drug product to the activity profile of approved and other existing antibacterial drug products with the same mechanism of action to assess the possibility of cross-resistance. Sponsors should present results from studies evaluating cross-resistance in tabular form with the following headings:

- Genera and species tested — species with unique mechanisms of resistance should be grouped separately; if serotype and/or genotype is known then that information should be included

- Drug product name

- MIC range — for each group of organisms and the number of isolates tested in each laboratory

- MIC_{50} range

- MIC_{90} range

- MBC

The complete study report, which includes stability and lot numbers of the drug product used for microbiological testing, and reproducibility of test results, should be submitted. If the data are derived from a publication, a copy of the publication should be included in the submission.

Under some circumstances, tentative inferences can be drawn about cross-resistance between antibacterial drug products within a specific population of isolates from regression analyses (i.e., MIC versus MIC or zone diameter versus zone diameter) of one drug product compared to another. In each of these situations, the evaluation should examine whether patterns with common levels of response to the antibacterial drug products are present. If cross-resistance exists between both test and control drug, a strong correlation between the MICs of both drug products would be expected to be observed; with a majority of the MICs clustered on a 45 degree diagonal. If resistance affects the activity of one drug product over the other, the cluster is usually skewed in the direction of one drug product or the other and away from the expected diagonal.

For an antibacterial with a novel mechanism of action, sponsors may not have detailed information available immediately on the mechanisms of action, resistance, or cross-resistance. As sponsors develop this information they should provide this information for review, ideally before phase 2. Applicants should provide in annual reports information that becomes available after approval relative to changes in resistance mechanisms for target pathogens. When such information warrants a change to the labeling for an antibacterial drug product, a labeling supplement should be submitted.[8]

E. Susceptibility Test Methods and Detection of Resistant Organisms

Sponsors should describe the methods used for generating susceptibility data. If a recognized reference method is used, sponsors can reference the standard method.[9] However, if susceptibility data are obtained by modification of a standard method, or by other methods, sponsors should provide a detailed description of the method, including the justification for the modification of the method, the effect on susceptibility results, and validation of the method. Modifications can include the addition of any substance (e.g., blood, body fluids, polysorbate). In some cases, isolates obtained during clinical trials may need to be tested for their susceptibility in the presence and absence of the substance and the results of both methods correlated with clinical and microbiological results. Sponsors should discuss any modification of an established in vitro susceptibility test method with the FDA before implementation in the drug development program. Sponsors also should conduct studies to address the influence of the growth medium (e.g., pH, divalent cations), inoculum density, incubation conditions (e.g., concentration of CO_2), and additives (e.g., polysorbate), in both broth and agar medium on in vitro susceptibility test results.

If sponsors propose to use freeze-dried panels to assess the MIC of clinical isolates during clinical trials, they should conduct a comparative study to demonstrate comparability of MIC results for the frozen and freeze-dried panels. Sponsors should discuss this proposed study with the review division to ensure that they develop appropriate data for the equivalency assessment. Upon completion of this study, sponsors should provide a report to the FDA for review and comment before initiation of the phase 2 studies.

F. Development of QC Parameters for In Vitro Susceptibility Testing

QC parameters for in vitro antibacterial susceptibility tests should be established before determining the activity of the antibacterial drug product against microorganisms to ensure the generation of precise, accurate, and reproducible results. These QC parameters should be determined during phase 1. If susceptibility information provided for microorganisms is obtained without proper quality monitoring, the test procedure and test results may be considered invalid. Routine QC procedures involve performance testing of designated QC strains that are genetically stable and have well-characterized susceptibility characteristics. Generally, the establishment of QC parameters should involve the use of 3 different lots of test medium, frozen panels in the case of MICs, 2 different lots of disks in the case of disk diffusion, and 10

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[8] See note 7, supra.

[9] Standard methods for susceptibility testing are developed by organizations such as the CLSI. Sponsors can describe the standard method that they have used by referencing a recognized testing methodology.

replicates of each QC strain over 3 days in at least 7 different laboratories. This testing is done to generate enough data points to determine appropriate QC parameters.[10]

Sponsors should obtain reference strains recognized by the FDA from a reputable source such as the American Type Culture Collection (ATCC). In the event that sponsors do not use the FDA-recommended QC organisms, they should justify the use of other strains and use well-characterized organisms or characterize them thoroughly. If a QC microorganism is chosen that is different from an existing FDA-recommended QC microorganism, it should be deposited in a recognized culture collection (e.g., ATCC).

G. Development of Interpretive Criteria for In Vitro MIC and Disk Diffusion Susceptibility Testing

The purpose of establishing susceptibility test interpretive criteria is to assist in the selection of antibacterial options that are appropriate for treatment of clinical infections.

Sponsors should consider the following information when establishing susceptibility test interpretive criteria: (1) in vitro microbiology data that include distributions of MICs or zone diameters obtained when the antibacterial is tested against a population of recent clinical isolates that are the target pathogens for the antibacterial; (2) data from animal models of infection including PK/PD information that describes the attainable concentrations of the antibacterial over time at the site of infection and/or the plasma and how these concentrations relate to killing or inhibition relative to the MIC of the target pathogen; and (3) correlation of the MIC or zone diameter with clinical and microbiological outcome when the antibacterial is used to treat infections during adequate and well-controlled clinical trials. Usually, the susceptibility test interpretive criteria that are included in labeling are limited to the MIC or zone diameters with which there is adequate clinical experience during clinical trials.[11]

H. Antibacterial Interactions and Fixed Combination Studies

Drug interaction studies of antibacterial drug products may provide information (e.g., synergy, antagonism, indifference) on the effects one antibacterial drug product may have on another. The synergistic or antagonistic activity of antibacterial drug products usually can be determined by in vitro studies of the interactions when the activity cannot be accurately anticipated from general knowledge of the drug product characteristics. Sponsors can conduct qualitative or quantitative in vitro studies using several methods developed to assess such potential drug interactions. These methods can include checkerboard titration analyzed by fractional inhibitory concentration, and kill curves. Kill curve characterization of antibacterial interactions is the preferred method for determining interactions. These drug interactions are particularly important for fixed combination drug products, including drug products that contain an antibacterial drug product and a component that counteracts a resistance mechanism (e.g., ß-lactam and ß-lactamase inhibitor combination). For these combinations, we recommend that sponsors provide

[10] For additional information, see *Development of In Vitro Testing Criteria and Quality Control Parameters; Approved Standard*, 2009, CLSI document M23-A3.

[11] Ibid.

the in vitro and/or in vivo data to support the contribution of each of the drug products to the activity. It is important to rule out antagonism.

I. Other Effects of Antibacterial Drug Product

Individual antibacterial drug products may have various effects on target bacteria and/or interactions with the host. These phenomena include, but are not limited to, postantibiotic effect (PAE), postantibiotic leukocyte effect, sub-MIC effects, effects on endotoxin, effects on virulence factors, and interactions with the host immune system. Although the clinical significance of these phenomena is not well understood, sponsors should provide this information as part of the overall understanding of the potential activity of an antibacterial drug product.

IV. ANIMAL MODELS OF INFECTION, HUMAN STUDIES AND CLINICAL TRIALS

This section describes the in vivo activity (therapeutic or prophylactic) and pharmacological studies in animal models of infection that mimic human disease and the pharmacological and phase 2 studies and clinical trials in humans. These data from animal models, pharmacological studies, and phase 2 studies and clinical trials (i.e., pharmacokinetics and pharmacodynamics) can be used to define and justify the dosing regimen used in phase 3 clinical trials and to establish provisional interpretive susceptibility criteria as described in section V. Available study reports including the details of the experimental design, the data, and their analyses should be submitted to the IND as soon as the information is available but before initiation of phase 3 clinical trials. It is important that proper doses be selected for the phase 3 clinical trials.

A. Animal Therapeutic and Pharmacological Studies

Since in vitro activity of antibacterial drug products may not translate into significant activity in vivo, sponsors should consider the use of appropriate animal models of infection for systemic antibacterial drug products when studying the PK/PD and activity of antibacterial drug products. Ideally, the animal models used will mimic the infection of interest and the pharmacokinetics of the drug product in humans. When developing an animal model to evaluate activity of an antibacterial drug product, sponsors should at a minimum obtain information on: (1) the natural history of the disease or condition in humans and animals; (2) the etiologic agent; and (3) the proposed intervention. Consideration of these factors will aid in determining if the antibacterial will be reasonably likely to produce clinical benefit in humans.

One objective of these experiments is to provide information relative to the selection of the clinical dose for trials in humans. Sponsors can consider use of allometric scaling to appropriately calculate a dose for humans that is equivalent to an effective dose in the animal model.

Animal models of human disease also can provide information on the potential efficacy and safety of antibacterial drug products in humans. Animal studies also may help to elucidate the nature of the disease process as well as its etiology, progression, and prevention. These studies can include a positive control along with a negative control. When developing a drug product for the treatment of pathogens resistant to an antibacterial drug product or possessing specific virulence factors, sponsors should attempt to evaluate efficacy in an appropriate animal model. In the case of a new molecular entity, we recommend that sponsors compare the antibacterial under development to an FDA-approved antibacterial drug product for the same indication. Comparison of the data for the antibacterial drug product under development to data for the FDA-approved antibacterial may provide insight into the ability of the antibacterial under development to treat infections.

Most commonly, the first in vivo testing or screening of an antibacterial drug product is the mouse protection evaluation. This model can determine whether an antibacterial drug product has in vivo activity and demonstrates whether a drug product is active when dosed orally or by a parenteral route. In addition to measuring survival, bacterial burden in blood and relevant affected organs should be measured. Sponsors can conduct comparative studies of the test antibacterial drug product with other antibacterial drug products exhibiting the same mechanism of action or drug products with the same spectrum of activity using the mouse protection test against key organisms. Results can be reported as 50 percent effective dose (ED_{50}), 50 percent protective dose (PD_{50}), or 50 percent curative dose (CD_{50}) calculated by the probit or Reed and Muench method. The bacterial burden should also be included.

We recommend that sponsors provide the scientific rationale for the selection and use of animal models for review and comment before initiating these studies.

B. Human Pharmacological Studies and Clinical Trials

1. Pharmacokinetics

Information from studies and clinical trials evaluating human clinical pharmacology of the investigational drug product can provide information on dose selection and likely antibacterial spectrum of activity based upon achievable exposures. Pathogenic microorganisms may invade various anatomical sites during infections. These anatomical sites may exist as distinct pharmacokinetic compartments, each with a different concentration of the antibacterial. To be effective, antibacterial drug products should distribute to the infection site in sufficient concentration and for a sufficient amount of time. Therefore, the infections for which a drug product may be useful may be dependent on its distribution characteristics. The pharmacokinetic information reported from human clinical pharmacology studies and clinical trials should include C_{max}, T_{max}, half-life, area under the curve, and a graphical presentation of drug serum concentrations for each subject at each sampling time. Data from Monte Carlo simulations predicting exposure and target attainment for relevant pharmacokinetic parameters should be included when available. We also recommend that sponsors characterize the pharmacokinetics of microbiologically active metabolites and present the data in a similar format as the parent drug.

Some antibacterial drug products may be inactive when protein bound, or there may be insufficient free active drug product at trough concentrations. Therefore, we recommend that sponsors characterize the effects of human serum proteins and other human body fluids (e.g., lung surfactant) when appropriate on the in vitro and in vivo activity of the drug product and its metabolites. The effects of human serum proteins and other human body fluids on activity of the drug product should be evaluated over the range of clinically relevant concentrations for the antibacterial drug product.

2. Pharmacodynamics

Sponsors should provide data available from human studies and clinical trials evaluating pharmacokinetic and pharmacodynamic responses. Information from studies and clinical trials evaluating human PK/PD can help in defining antibacterial spectrum of activity based upon exposures attained and the response that is generated. Such information also can be helpful for dose selection.

Insight can be obtained into the potential activity of an antibacterial drug product by reviewing data on the following:

- Concentration-response relationships
- Time-dependent activity
- Time-kill synergy data
- Tolerance, persistence, and skip tube phenomena

These data should be generated using organisms representative of a number of different genera and species targeted by the antibacterial as well as a number of isolates of the same species. The data for bound and free antimicrobial concentrations should be presented in tabular form and in graphical form, where appropriate (e.g., concentration-response activity).

V. ESTABLISHING PROVISIONAL INTERPRETIVE CRITERIA

Provisional interpretive criteria are the interpretive criteria that are used based upon the limited information that is available before the initiation of phase 3 clinical trials. There are two main approaches for establishing provisional interpretive criteria. The first approach is to provide data that support the use of interpretive criteria for a related drug product that has been shown to correlate with the available data for the investigational drug product. For the second approach, when available data do not support an adequate correlation between the investigational drug product and a similar drug product for which interpretive criteria have already been established, sponsors should use interpretive criteria for the investigational drug product, as described below. They should consider the mechanism of action of the test antibacterials and other drug products with the same mechanism of action when establishing susceptibility testing methods and interpretive criteria.

Sponsors should provide comparative data generated with a representative battery of FDA-approved antibacterials having the same mechanism of action to justify the need for separate interpretive criteria and testing for the new drug product when existing susceptibility testing procedures and interpretive criteria may suffice. The data should include testing of at least 500 isolates relevant to the target pathogens for the indications being sought. Sponsors should provide testing data on a sufficient range of clinically relevant species to allow conclusions to be made regarding the potential clinical efficacy of the antibacterial for the intended indication. Sponsors should identify the prominent genotypes, serotypes, biotypes, and isolates with known mechanisms of resistance and include these in the test panel. When appropriate, the spectrum of activity against hetero-resistant microorganisms should be determined (e.g., vancomycin hetero-resistant *S. aureus*). The organisms tested should be clinical isolates with susceptibility profiles that are representative of antibacterial drug products used to treat infections caused by the target pathogens for the indication being sought.

The data justifying updated susceptibility testing criteria should be presented as regressions of MIC versus MIC and zone diameter versus zone diameter. These data should be examined for clusters of isolates that are substantially different from those clusters near the expected regression line of MIC versus MIC or zone versus zone plots. For example, a cluster in a position away from the expected regression line suggests that one of the drug products is affected by a resistance mechanism that does not affect the other drug product. Therefore, the two drug products are not interchangeable, and new testing procedures and interpretive criteria are justifiable for the new drug product. When developing an antibacterial with a specific mechanism of action for the treatment of pathogens resistant to other antibacterials with the same mechanism of action, these types of analyses can be extremely useful in demonstrating the activity of the new drug product.

If sponsors justify the need for new susceptibility testing interpretive criteria, the raw data should be analyzed in terms of frequency distributions (e.g., histograms) of susceptibility test results. Frequency distribution analyses can help define which populations of isolates harbor specific resistance mechanisms that sponsors should identify in the laboratory. We recommend that preliminary breakpoints exclude groups of potentially resistant populations from the *susceptible* category when they exist. Frequency distributions can be analyzed for both dilution and diffusion susceptibility testing methods. Frequency distributions call for evaluation for each target species of microorganism, especially if there is not a clear demarcation between the resistant and susceptible populations.

Evaluation of the frequency distribution analyses relative to the pharmacokinetics and pharmacodynamics of the antibacterial can further refine the preliminary breakpoints.

Additional adjustments to the provisional interpretive criteria can be considered to accommodate methodological variability between diffusion and dilution susceptibility testing methods. Sponsors also can suggest adjustments to provisional interpretive criteria by evaluating scattergrams of dilution testing results compared with diffusion testing results of the same isolates tested with both methods. This evaluation can be performed by the Error Rate Bounding method that compares diffusion testing to dilution testing.[12] The computational algorithm generates interpretive criteria that minimize the number of isolates with diffusion testing results that fall outside the provisional interpretive criteria of the dilution testing results. Final

[12] CLSI, 2009, *Development of In Vitro Testing Criteria and Quality Control Parameters; Approved Standard*, CLSI document M23-A3.

interpretive criteria should be determined only after completion of the pertinent clinical trials (see section VII).

VI. CLINICAL TRIAL PROTOCOLS

The evaluation of microbiological data from clinical trials is dependent on the isolation of a causative pathogen from a target site of infection. When a causative pathogen has been isolated, additional analyses can be performed to determine its susceptibility to the test drug using standardized in vitro test methods. We recommend that a central laboratory be used for microbiologic testing during clinical trials. The name of the central laboratory or any other laboratories used should be specified. We strongly recommend that sponsors provide clinical trial protocols for review and comment before trial initiation.

VII. ESTABLISHMENT OF FINAL QC PARAMETERS AND INTERPRETIVE CRITERIA

At the time of NDA submission, applicants should propose interpretive criteria for the bacteria listed in the INDICATIONS AND USAGE section of the labeling. The proposed interpretive criteria should take into consideration the information collected throughout the drug development program including the following:

- Microbiologic eradication and clinical response to therapy in clinical trials based upon individual indication, organism type, specific virulence factors, and susceptibility test results

- Available human and animal data on pharmacokinetics and pharmacodynamics

- Acceptability of susceptibility test QC parameters

A. Susceptibility Test QC Data

The use of established methods and concomitant use of QC strains lends confidence to the in vitro susceptibility data generated from the testing of isolates. Therefore, QC data should be provided with all susceptibility test results done on isolates at each facility that is conducting susceptibility testing for clinical trials. Alternatively, if in vitro susceptibility trials are conducted by a central laboratory, we recommend that applicants provide the QC data generated by the central laboratory. Failure to provide QC information may invalidate the susceptibility test results. In addition, we recommend that applicants analyze the QC data generated during the conduct of clinical trials to determine whether adjustments to the QC ranges are necessary.

B. Establishing Final Interpretive Criteria for Use in Labeling

Section V describes how provisional interpretive criteria for use in phase 2 and phase 3 clinical trials can be established. Provisional interpretive criteria are based upon the limited information that is available at early stages of drug development; the criteria may need to be refined based upon findings from additional data (e.g., clinical trials). Therefore, we recommend that the applicant evaluate whether the clinical and microbial eradication outcomes support the provisional interpretive criteria. The applicant should perform an analysis of the correlation between the clinical cure and microbial eradication rates with the proposed in vitro test results interpretive criteria to determine their clinical relevance. When appropriate, the clinical and microbial eradication rates should be presented as overall rates and as individual rates against microorganisms with specific resistances to other antimicrobials as well as specific virulence factors. These analyses should be part of the NDA submission and should form the basis for the final selection of interpretive criteria.

We recommend that the results of all associated susceptibility tests within the microbiology section of the NDA be provided in electronic format (see section VIII). Applicants should augment the electronic database by designated summary tables and interpretations identified below. Where possible, the database should include both zone diameters and MICs for each isolate.

We recommend a single electronic database formatted from the clinical trials with the subject-by-subject data presented in columns. Each column heading should identify the scope of information below it. For instance, a subject ID number can include a coding arrangement that differentiates the trial center as well as the individual subject. We recommend that the following information be provided in the database under appropriate columnar headings:

- Center number

- Subject ID number

- Treatment group

- Sample source

- Species of bacterial isolate

- Indication

- Subject-by-subject clinical evaluations including separate rows for each subject, the subject's status of microbiological eradication, and the subject's overall clinical response (e.g., cure, fail)

- Susceptibility test results by diffusion methods for the test drug and the comparator drug

- Susceptibility test results by dilution methods for the test drug and the comparator drug

Applicants should discuss with the division at the time of the pre-new drug application (pre-NDA) meeting the format of the microbiology datasets.

Using the data included in the electronic database, applicants should provide an interpretation of the data described below for test and comparator drugs. Because of possible geographic differences in antibiograms and the clonal nature of pathogens, data should be presented in both combined (i.e., United States and non-U.S.) and separate (i.e., United States and non-U.S. in separate tables) formats. Where appropriate, we recommend that U.S. data be broken down into regions (e.g., Northeast, Southeast, Midwest, Northwest, Southwest) with non-U.S. data additionally broken down by region (e.g., Asia, Europe, Africa), and within region by country (e.g., France, Germany).

We recommend that the following be listed:

1. MIC values and subject <u>microbiological</u> responses for each baseline pathogen within each proposed indication. Applicants should list all subsets of organisms demonstrating unique mechanisms of resistance (e.g., methicillin-resistant *S. aureus*, beta-lactamase-positive *Haemophilus influenzae*) and virulence (e.g., PVL genes) separately.

2. MIC values and subject <u>clinical</u> response for each baseline pathogen for each proposed indication. Applicants should list all subsets of organisms demonstrating unique mechanisms of resistance (e.g., methicillin-resistant *S. aureus*, beta-lactamase-positive *H. influenzae*), and virulence (e.g., PVL genes) separately.

3. Zone diameter values and subject <u>microbiological</u> responses for each pathogen for each proposed indication. Applicants should list all subsets of organisms demonstrating unique mechanisms of resistance (e.g., methicillin-resistant *S. aureus* beta-lactamase-positive *H. influenzae*), and virulence (e.g., PVL genes) separately.

4. Zone diameter values and subject <u>clinical</u> responses for each pathogen for each proposed indication. Applicants should list all subsets of organisms demonstrating unique mechanisms of resistance (e.g., methicillin-resistant *S. aureus*, beta-lactamase-positive *H. influenzae*), and virulence (e.g., PVL genes) separately.

5. For each subset of pathogens requiring defined MIC breakpoints, all individual isolates in the range of MICs from two dilutions below the susceptible and two dilutions above the resistant provisional breakpoints.

6. For each subset of pathogens requiring defined zone diameter breakpoints, all individual isolates in the range of zone diameters from 4 to 6 millimeters above the susceptible and 4 to 6 millimeters below the resistant provisional breakpoints.

7. By indication and pathogens relevant to indication, all MICs for isolates associated with microbial failures. The pathogen should be identified to the species level.

8. By indication and pathogens relevant to indication, all zone diameters for isolates associated with microbiological failures. The pathogen should be identified to the species level.

9. For each organism (e.g., nonfastidious, fastidious, and anaerobic), the MIC value indicating the number and percent of isolates at that MIC associated with each microbiological response. MIC values should be grouped by organism type.

10. For each organism (e.g., nonfastidious, fastidious), the zone diameter indicating the number and percent of isolates at the zone diameter associated with each microbiological response. Zone diameter information should be grouped by organism type.

11. For each group of organisms, a histogram showing the number of isolates at each MIC from clinical trials overlaying isolates from nonclinical studies. Applicants should present organisms with characterized phenotypic resistance and virulence markers as a subset.

12. For each group of organisms, a histogram showing the number of isolates at each zone diameter from clinical trials overlaying isolates from nonclinical studies. Applicants should present organisms with characterized phenotypic resistance and virulence markers as a subset.

The interpretive criteria proposed for the labeling should be the product of the analyses of all relevant nonclinical and clinical bacteriology data collected during drug product development.

C. First and Second Lists of Target Pathogens in Labeling

The Microbiology subsection of the labeling contains two lists of organisms.

The first list is based on pathogens evaluated during clinical trials that are included in the INDICATIONS AND USAGE section of the labeling. Applicants should format this section as described in Appendix A.

The second list is based on the relevance of the organism to the indication and its susceptibility to concentrations of the antibacterial that can be achieved using the proposed dosage. The inclusion of organisms in the second list is not based on results from adequate and well-controlled clinical trials. Applicants should provide information in support of the second list in the form of a summary for each species proposed for inclusion by indication. The summary should include:

- A discussion of the relevance of each pathogen to a specific clinical indication

- The frequency in which the pathogen is shown to cause disease in the general population

- Relevant literature reference and/or laboratory test data summary tabulations (e.g., range, MIC_{50}, MIC_{90}) of the susceptibility data of the pathogen and annotated supporting literature

- In vitro susceptibility information for at least 100 isolates (e.g., range, MIC_{50}, MIC_{90}) of each organism proposed for the second list (see section III for characteristics of organisms that should be included for testing)

- A discussion of the methods used and their comparability to assess susceptibility as described in the supporting literature

- Comparisons of U.S. and foreign data analyzed separately and together

- Susceptibility data that are accompanied by the appropriate QC data

Microorganisms included in the second list should have MIC_{90} values less than or equal to the clinically relevant susceptible breakpoint established for the particular genera, species, or Family of microorganism related to a specific indication or indications.

The following factors should be considered in the development of this second list:

- Certain microorganisms are disease specific and therefore can be properly placed only in the first list. Examples of such microorganisms are *Mycobacterium tuberculosis*, *Bacillus anthracis*, *Mycobacterium leprae*, *Yersinia pestis*, *Neisseria meningitidis*, *Neisseria gonorrhoeae*, and *Brucella species*.

- There should be scientific evidence demonstrating that a microorganism is a frequent pathogen for an indication for which approval is being sought. For example, applicants can support inclusion of a particular pathogen by providing a reasonable number of associated and adequately described clinical cases published in the scientific literature.

- Applicants should support the species included in the second list with susceptibility test results of recent clinical isolates (MICs) correlated with the achievable concentrations of the antibacterial using the recommended dosing regimen (see sections VII.D. and VII.E.).

D. New Molecular Entities

If the antibacterial drug product is a new molecular entity, we recommend that the isolates used to generate the data span no more than 3 years from the date of NDA submission. For common species, we recommend that applicants provide data for at least 500 isolates from broad geographic regions of the United States. See section V for a discussion of the characteristics of the organisms that should be tested. Less frequently occurring isolates may warrant lower numbers. If applicants also have foreign in vitro susceptibility data, the data should be presented separately from U.S. data. Only 25 percent of the isolates used to make the assessment of inclusion in the second list should come from foreign studies. Applicants should describe in detail the susceptibility test methods used or reference a standard method if one is used for isolates from foreign studies. Consideration of foreign data is usually based on the comparability of the organisms in relation to antimicrobial susceptibility profiles, serotypes, genotypes, and virulence factors to the same microorganism in the United States, and comparability of methods used to generate susceptibility data. The distribution of MIC data from these isolates can provide useful information to monitor changes in the susceptibility profile after a drug product is marketed.

E. New Use for an FDA-Approved Drug

If the NDA is for a drug product containing a drug substance that has already been approved for another use or in another drug product, we recommend that the applicant provide relevant and comprehensive surveillance data and data from published literature. Because resistance rates generally increase over time with use of the antibacterial drug product, results from more recent studies generally are of greater importance. For surveillance data, we recommend that the applicant provide the name of the organization conducting the studies, pertinent standard operating procedures, and the geographic origin of the data. Literature from refereed journals that can provide the origins of the isolates (i.e., geographic region of origin and reference lab that performed the testing), test methods used, and QC methods can provide useful surveillance data. We recommend that applicants provide publications that provide an overview of MIC ranges, MIC_{50}, MIC_{90}, and histograms.

VIII. LOCATION IN THE ELECTRONIC COMMON TECHNICAL DOCUMENT FOR MICROBIOLOGY INFORMATION

We strongly suggest that applicants provide microbiology information in the electronic common technical document (eCTD) as described in the guidance for industry *Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*.[13] Generally, the information on microbiology should be provided in two sections of the eCTD as follows:

- Module 2, Section 2.7, Clinical Summary, subsection 2.7.2.4, Special Studies. This section should contain the microbiology <u>summary report</u> that contains the type of information with associated subheadings as described in this guidance. Thus, it contains the information used to justify the microbiology information included in the labeling.

- Module 5, Clinical Study Reports, subsection 5.3.5.4, Other Study Reports. This section should contain the nonclinical study and clinical trial <u>reports</u> used in the construction of the summary information provided in subsection 2.7.2.4. All of the study and trial reports used to construct the summary report presented in section 2.7.2.4 should be cross-linked to the summary report. Both of these sections should be cross-referenced to each other.

[13] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

Microbiology data should be provided cumulatively over the history of the application, including during the investigational stages of drug product development. Each data submission should be identified by submission date.

IX. REVISION OF EXISTING SUSCEPTIBILITY TESTING METHOD, QC PARAMETERS, OR INTERPRETIVE CRITERIA

Over time, additional information may become available regarding the methods for in vitro susceptibility testing and/or the QC parameters used to monitor the performance of the test as well as how the susceptibility test results should be interpreted. Consequently, it is important that the in vitro antibacterial susceptibility testing methods, the QC parameters, and the antibacterial susceptibility test interpretive criteria listed in the labeling be reviewed on a regular basis and updated to reflect the most current information. Any changes in the in vitro susceptibility test method, QC parameters, or interpretive criteria should be indicated in the annual report. The procedures for updating microbiology labeling information can be found in the guidance for industry *Updating Labeling for Susceptibility Test Information in Systemic Antibacterial Drug Products and Antimicrobial Susceptibility Testing Devices*. The guidance describes two approaches for updating microbiology information in the labeling: application holders can submit a labeling supplement that relies upon a standard recognized by the FDA or submit a labeling supplement that includes data supporting a proposed change to the microbiology information in the labeling. [14] For applicants that choose to update the labeling based upon the latter approach, submitting a labeling supplement with supporting data, the following types of data should be submitted for each of the types of changes in the labeling.

- **Change in susceptibility testing method.** The following information, at a minimum, should be presented for review when submitting information relevant to changes in the susceptibility testing method:

  - Rationale for change
  - Description of the old and new methods with changes noted
  - Validation data for the new method
  - QC parameters for the new method

  Any change to a test method (e.g., microbroth dilution) should be accompanied by data to show that the results correlate with other methods (e.g., agar dilution, disk diffusion testing) by which susceptibility testing can be done.

- **Changes in susceptibility testing QC parameters.** The following information, at a minimum, should be presented for review when submitting information relevant to changing QC parameters:

[14] In addition, the guidance describes an option to provide a written justification if the FDA has recognized a standard that differs from the approved microbiology labeling and an applicant believes that changes to the microbiology labeling are not needed for a particular drug product.

- Rationale for change
- Results of studies validating the change in the QC parameters

For additional details on establishing susceptibility test QC parameters, see CLSI document M23-A3.[15] See section 10 for information on establishing QC parameters.

- **Changes in susceptibility test interpretive criteria.** The susceptibility of certain microorganisms to antibacterial drug products may change over time. Information relevant to changes may include additional data on susceptibility of microorganisms and response to therapy and/or new mechanisms of resistance in microorganisms that result in decreased susceptibility to a particular antimicrobial drug product. Changes in antimicrobial susceptibility may translate into a lack of efficacy and/or safety concerns when out-of-date antimicrobial susceptibility information leads to failure to appropriately treat the indicated infection.

  The following information at a minimum should be submitted for changing existing susceptibility test interpretive criteria:

  - Rationale for change
  - Microbiological data

    - Showing the MIC and zone size distributions against the genera and species of interest; data should be from isolates collected in the preceding 3 years of the submission

    - Presented so that susceptibility to the antimicrobial can be visualized to determine microbiologically supported cut-offs (e.g., histograms)

    - Providing the relationship between the MIC and disk diffusion zone diameter in graphical form so the effect of proposed changes in interpretive criteria on the categorical agreements between the two methods can be seen

    - Using the error-rate bounded method of Metzler and DeHaan[16] to determine discrepancies between the two methods; the Metzler and DeHaan method usually needs to be modified[17] because two MIC values are normally described to define an *intermediate* category

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[15] CLSI, 2009, *Development of In Vitro Testing Criteria and Quality Control Parameters; Approved Standard*, CLSI document M23-A3.

[16] Metzler, DM and RM DeHaan, 1974, Susceptibility Tests of Anaerobic Bacteria: Statistical and Clinical Considerations, J Infect Dis, 130:588-594.

[17] Bruden, MN, GE Zurenko et al., 1992, Modification of the Error-Bounded Classification Scheme for Use with Two MIC Breakpoints, Diagn Microbiol Inf Dis, 15:135-140.

- Human pharmacological data

  - Human PK/PD data as described in section IV.B.
  - Target attainment rates for each MIC value provided in graphical format
  - Details of modeling
  - Whether exposure-response relationships exist (e.g., Monte Carlo simulation)
  - The source of PK data

- Clinical data[18]

  - From trial reports of adequate and well-controlled trials when available
  - From clinical trials reported in the literature or case-control studies
  - From observational studies, meta-analysis, and case series

Literature reports of single cases providing information on clinical failures related to existing breakpoints generally will not be sufficient to change breakpoints, but may serve as reason to initiate additional evaluation of the situation. The data upon which the existing breakpoints were determined should be re-evaluated whenever possible in light of the new information. We recommend that information for revision of breakpoints should be presented in a manner similar to what is described in this guidance.

[18] We recognize that it may be difficult to obtain adequate and well-controlled trials from which clinical efficacy and microbiological eradication data can be taken to support the revision of breakpoints. However, applicants should provide as much clinical response data whenever possible to support revision of breakpoints. We recognize that each revision review may need to be evaluated with different types of data and perhaps different weight given to different types of data.

REFERENCES

CLSI, 1999, *Methods for Determining Bactericidal Activity of Antimicrobial Agents; Approved Guideline*, CLSI document M26A.

CLSI, 2007, *Methods for Antimicrobial Testing of Anaerobic Bacteria; Approved Standard*, CLSI document M11-A7.

CLSI, 2009, *Development of In Vitro Testing Criteria and Quality Control Parameters; Approved Standard*, CLSI document M23-A3.

CLSI, 2009, *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard*, CLSI document M07-A7.

CLSI, 2009, *Performance Standards for Antimicrobial Disk Susceptibility Tests; Approved Standard*, CLSI document M02-A10.

CLSI, 2009, *Performance Standards for Antimicrobial Susceptibility Testing; 19th Informational Supplement*, CLSI document M100-S19.

Turnridge, J and DL Paterson, 2007, Setting and Revising Antibacterial Susceptibility Breakpoints, Clinical Microbiology Reviews, Vol. 20, pg. 391-408.

APPENDIX A: EXAMPLE FORMAT FOR THE MICROBIOLOGY SUBSECTION OF LABELING

As provided for in the final rule Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, the microbiology portion of the labeling can be added as subsection 12.4.[19]

This Appendix contains an example of a format for the Microbiology subsection of the labeling. We recommend that applicants include in the Microbiology subsection of the labeling, at a minimum, the information identified with an asterisk (*).

12.4 Microbiology*

> ***Editorial Note:*** *Applicants can place relevant microbiological information that provides additional characterization of the antimicrobial drug product here and under the following categories. The editorial notes are informational and are not part of the labeling.*

*Mechanism of Action**

*Mechanism of Resistance**

<u>Interaction with Other Antimicrobials</u>

<u>Other</u> [Relevant information to be determined on a case-to-case basis]

*Lists of Microorganisms**
[Generic name of drug] has been shown to be active against most isolates of the following microorganisms, both in vitro and in clinical infections as described in the INDICATIONS AND USAGE section:* Each organism is specifically associated with an indication in the INDICATIONS AND USAGE section (e.g., *S. aureus* – Complicated Skin and Skin Structure Infections) if there is more than one indication.

[List organisms under the following categories in alphabetical order]

<u>Gram-positive bacteria</u>*
<u>Gram-negative bacteria</u>*
<u>Anaerobic bacteria</u>*
<u>Other microorganisms</u>*

The following in vitro data are available, <u>**but their clinical significance is unknown**</u>.* At least 90 percent of the following bacteria exhibit an in vitro minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for [generic name of drug]. However, the

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[19] See 71 FR 3922 and 21 CFR parts 201, 314, and 601.

efficacy of [generic name of drug] in treating clinical infections due to these bacteria **has not been** established in adequate and well-controlled clinical trials.*

[List organisms under the following categories in alphabetical order]

Gram-positive bacteria*
Gram-negative bacteria*
Anaerobic bacteria*
Other microorganisms*

> ***Editorial Note:*** *For an organism to become part of the above list of organisms, the organism at a minimum should: (1) be relevant to an indication granted in the labeling; and (2) have an MIC_{90} below the concentration of the antimicrobial achievable in the plasma or at the infection site using the dosing regimen approved in the labeling as determined from testing at least 100 isolates of the organism.*

*Susceptibility Test Methods**

When available, the clinical microbiology laboratory should provide the results of in vitro susceptibility test results for antimicrobial drug products used in resident hospitals to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug product for treatment.*

> ***Editorial Note:*** *If standardized susceptibility test methods are not used (see example references 1, 2, 3, and 4 at the end of Appendix A), information and unusual characteristics of the antimicrobial drug product susceptibility testing procedure can be placed under the susceptibility test method that is pertinent.*

Dilution techniques:*

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized test method[1,2] (broth and/or agar). The MIC values should be interpreted according to criteria provided in Table 1.*

> ***Editorial Note:*** *See an example of Table 1 at the end of Appendix A.*

Diffusion techniques:*

Quantitative methods that require measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized test method.[2,3] This procedure uses paper disks impregnated with [x] mcg [generic name of drug] to test the susceptibility of microorganisms to [generic name of drug]. The disc diffusion interpretive criteria are provided in Table 1.*

Anaerobic techniques:*

For anaerobic bacteria, the susceptibility to [generic name of drug] can be determined by a standardized test method.[4] The MIC values obtained should be interpreted according to the criteria provided in Table 1.*

A report of *Susceptible* indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentrations at the infection site necessary to inhibit growth of the pathogen. A report of *Intermediate* indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug product is physiologically concentrated or in situations where a high dosage of the drug product can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of *Resistant* indicates that the antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentrations usually achievable at the infection site; other therapy should be selected.*

Quality Control:*

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test.[1,2,3,4] Standard [generic name of drug] powder should provide the following range of MIC values noted in Table 2.* For the diffusion technique using the [disk content of antimicrobial] mcg disk, the criteria in Table 2 should be achieved.

Editorial Note: *See an example of Table 2 at the end of Appendix A.*

Example Tables and References for Appendix A

Editorial Note*: The following table and footnote are provided as examples of information that applicants can provide in the labeling.*

Table 1. Susceptibility Test Interpretive Criteria for [generic name of drug]*

Pathogen	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameters in mm)		
	S	I	R[a]	S	I	R[a]
Pathogen #1	< #	#-#	>#	>#	#-#	<#
Pathogen #2	<#	#-#	>#	>#	#-#	<#
etc.	etc.			etc.		

[a] If there are no resistant criteria because of the lack of data on resistant microorganisms, the following should be noted in the labeling: "The current absence of data on resistant isolates precludes defining any category other than 'Susceptible.' If isolates yield MIC results other than susceptible, they should be submitted to a reference laboratory for additional testing."

Table 2. Acceptable Quality Control Ranges for [generic name of drug]*

QC Strain	Minimum Inhibitory (mcg/mL)	Disk Diffusion (zone diameter in mm)
QC Strain #1	#-#	#-#
QC Strain #2	#-#	#-#
etc.	etc.	etc.

Editorial Note: *Include Table 2 when appropriate QC parameters should be provided for both broth and agar MIC tests.*

References (Use applicable references)

Editorial Note: *References should go in section 15 of the labeling.*

1. Clinical and Laboratory Standards Institute (CLSI). Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically. CLSI document M07-A#. CLSI, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, (Year).

2. CLSI. Informational Supplement. CLSI Document M100-S####. CLSI, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, (Year).

3. CLSI. Performance Standards for Antimicrobial Disk Susceptibility Tests. CLSI document M02-A#. CLSI, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, (Year).

4. CLSI. Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria. CLSI document M11-A#. CLSI, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, (Year).

APPENDIX B: EXAMPLE TIMELINE FOR SUBMISSION OF DATA TO IND AND NDA

As described in this guidance, we recommend that information pertinent to the development of systemic antibacterial drug products be submitted in a manner that allows the review to be timely in the progression of drug development. As an example, data used to develop proposed QC parameters for susceptibility testing should be submitted before human phase 2 clinical trials. This Appendix provides a timeline from the pre-investigational new drug application (pre-IND) through each of the three IND phases and the clinical microbiology information that should be provided during each phase. Although the timeline shows well-delineated phases, we recognize that work in several phases may be going on concurrently. It is important that the work in one phase does not rely on completion of work in a previous phase. For example, it would not be appropriate to test isolates of organisms from subjects in phase 2 if the QC parameters for susceptibility testing have not been established. The reader should consult the body of the guidance for specific details for each phase. We recommend that before proceeding with any study or clinical trial that the protocol be submitted for review and comment. It is helpful if submissions needing review by the FDA be sent in at least 6 to 8 weeks in advance of when a response is desired.

The timeline provides information relative to clinical microbiology and not to other disciplines.

Pre-IND — The pre-IND meeting is basically an information gathering session for both the FDA and the sponsor. Some of the areas that can be discussed are:

- General thoughts and concepts about the antimicrobial
- Preliminary thoughts on what indications are sought
- Information relative to the activity of the antimicrobial against what may be considered target pathogens
- Susceptibility test methods
- Pharmacokinetics of the drug product
- Design of phase 1 studies and submission of protocols

Phase 1 — Phase 1 studies for clinical microbiology generally include but are not limited to the following:

- Characterization of susceptibility test conditions that may influence susceptibility test results (e.g., cation concentration, pH)
- Establishment of in vitro susceptibility test QC parameters

- Determining what in vivo conditions may affect the activity of the antimicrobial (e.g., protein binding, effect of body fluids on activity of antimicrobial)

- Determining the spectrum of activity of the antimicrobial after test conditions and QC parameters have been defined

- Characterization of the pharmacokinetics and pharmacodynamics of the antimicrobial in animal models

- Determining the in vivo activity of the drug product in appropriate animal models against target pathogens

- Determining other characteristics of the antimicrobial (e.g., PAE, intracellular activity of the drug product)

- Design of phase 2 studies and submission of protocols

Phase 2 — Phase 2 studies incorporate limited testing in humans after the antimicrobial has been determined to be safe for administration, as follows:

- Determine pharmacokinetics in human subjects; consult the clinical pharmacology guidances for details[20]

- Evaluate available information on antimicrobial efficacy in humans

- Propose provisional breakpoints for phase 3 clinical trials

- Propose content for the Microbiology subsection of the labeling

- Design phase 3 clinical trials and submit protocols

Phase 3 — Phase 3 clinical trials involve determining the efficacy of the antimicrobial in adequate and well-controlled clinical trials.

Pre-NDA — This meeting between the applicant and the FDA is beneficial in determining if the NDA is appropriate to file and if so the format to be used for the NDA submission.

NDA — The NDA is the repository of the data obtained during the three IND phases with the most critical part being the results of the clinical trials conducted during phase 3.

Consult the body of this guidance for specifics on the information and data to be included and the format in which it is to be submitted.

[20] See http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.